DEVELOPMENT OF NANO-ELECTROCHEMICAL SENSORS FOR THE STUDY OF SELECTED MEDICINAL COMPOUNDS

A

SYNOPSIS

OF

RESEARCH WORK PROPOSED TO BE CARRIED OUT IN PERSUANCE OF THE REQUIREMENT FOR THE AWARD OF DEGREE OF

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ORIGIN OF THE PROBLEM

Pharmaceutical analysis belongs among the most rapidly developing areas of science. Since past decades, pharmaceutical research has played a key role in development of pharmaceuticals. At present, drug analysis and pharmaceutical impurities are the subjects of constant review in public interest. From the onset of official pharmaceutical analysis, analytical assay methods such titrimetry, spectrometry, chromatography, capillary electrophoresis and electroanalytical methods have been utilized to assess the quality of bulk drug materials.

The determination of pharmaceuticals by electroanalytical method is highly sensitive, selective, simple, rapid and cost effective, which make these methods suitable for routine analysis. Moreover, understanding of the redox mechanism is necessary to ensure perception and assessment of these pharmaceutical drugs, which gives an idea of in-vivo fate of drug as it is assumed that there is a similar redox mechanism of the drug shared at the surface of electrode and biological system.

A detailed survey of literature has revealed the wide applicability of electrochemical analysis of pharmaceutical drugs yet there are some pharmaceutical drugs which need to be explored by this technique.

The research work proposed in this synopsis is based on the combined advantages of nanomaterial based sensors and voltammetry with the aim to develop a stable sensor and to achieve lower limits of detection and quantification of the drugs. Various parameters such as effect of pH, potential, scan rate, types of surfactants (cationic, anionic or non-ionic) will be optimized using cyclic voltammetry and square-wave voltammetry. Validation of method in term of accuracy, precision, specificity and selectivity will be done. Thus present piece of work is focused mainly on the fabrication of a sensitive sensor for monitoring some organic compounds with medicinal properties.

ABBREVIATION

AAdSV	Anodic Adsorptive Stripping Voltammetry
BCPE	Bare Carbon Paste Electrode
BDDE	Boron Doped Diamond Electrode
CPE	Carbon Paste Electrode
CV	Cyclic Voltammetry
DME	Dropping Mercury Electrode
DPAdSV	Differential Pulse Adsorptive Stripping Voltammetry
DPP	Differential Pulse Polarography
DPV	Differential Pulse Voltammetry
GCE	Glassy carbon Electrode
GOx	Glucose oxide
GR	Graphene
HMDE	Hanging Mercury Drop Electrode
ILs	Ionic Liquids
mCPE	Modified carbon paste electrode
MIP	Molecularly imprinted polymer
MWCNT	Multi-Walled Carbon Nano Tube
PBC	Paper Based Electrode
P-Tol	Para Toluene
SWAdSV	Square Wave Adsorptive Stripping Voltammetry
SWCAdSV	Square Wave Cathodic Adsorptive Stripping Voltammetry
SWV	Square Wave Voltammetry
FA	Folic Acid
XRD	X-Ray Diffraction
FTIR	Fourier Transform Infrared
SEM	Scanning Electrode Microscopy
UV- VIS	Ultraviolet - Visible

INTRODUCTION

Pharmaceutical and biomedical analysis is one of the most important branches of applied analytical chemistry. The escalation in the demand of pharmaceuticals calls for higher level of quality control. There are chances that these pharmaceuticals may develop impurities at various processing stages, thus making them risky for administration. Therefore, development of a new analytical method seems appropriate for quantitative and qualitative investigation of bulk drug materials, the intermediates, drug impurities, biological samples containing drugs and their metabolites (Siddiqui et al. 2013; Bozal et al. 2011). Moreover, the newly developed drugs with high physiological activity are administered in smaller amounts, thus indicating the need for the development of a highly sensitive and selective analytical method (Patriarche and Zhang, 1990).

Among different analytical tools and techniques studied in chemistry, electrochemistry holds an important area in pharmacological studies. The electroanalytical chemistry is that area of analytical chemistry and electrochemistry which uses electrode as a probe, to measure something that directly or indirectly involves the electrode (Plambeck et al. 1982). The best known analytical techniques are the electrochemical methods which possesses the following advantages: easy instrumentation, moderate cost and portability, high speed, high scan rates, accuracy, and precision, large linear dynamic range with no pollution effect and insignificant effect of the matrix from endogenous substances in biological media or from excipients in pharmaceutical dosage forms (Kauffmann and Vire, 1993; Jain et al. 1997; Torres et al. 2002; Abdine and Belal, 2002; Santos et al. 2005; Jain et al. 2006; Silva et al. 2006; Sun and Zhang, 2007; Farghaly et al. 2014).

Voltammetry, among electrochemical methods, is a unique area of research which is defined as current-voltage technique where the applied potential is continuously varied at the electrode-solution interface and the resulting current is measured. Several examples in the literature report the existence of relationship between the voltammetry and pharmacological activity of the drugs (Kauffmann et al. 1985; Dakova et al. 1990; Kovacic et al. 1989; Ames et al. 1991) and the knowledge of their mechanism help us to understand the mechanism of interaction of drug with living cells (Ozkan et al. 2003; Kounaves, 1997).

In voltammetry, cyclic voltammetry (CV) plays an important role and is widely used to study a variety of redox reactions (Nicholson et. al. 1965), electron transfer kinetics (DuVall et. al. 1999), the reversibility of reactions (Bond et al. 1998), determine the electron stoichiometry of a system, and for formal reduction potential of an analyte. The reduction potential of an analyte can be used as an identification tool because concentration is proportional to current in a reversible Nernstian system. The Concentration of an unknown solution can be determined by generating a calibration curve of current vs. concentration (Carriedo et al. 1988). In cellular biology, potential is used to measure the concentrations in living beings (Wightman et al. 2006). In organometallic chemistry, it is used to evaluate redox mechanisms (Geiger W.E., 2011).

The development of chemical and biological sensors is currently one of the most active areas of analytical research. Sensors are small devices that incorporate a recognition element with a signal transducer. Such devices can be used for direct measurement of the analyte in the sample matrix (Zhang et al. 2008). It has been demonstrated that the use of solid electrodes depicts the most rapidly growing class of sensors. Moreover, the beauty of electrochemical techniques is to utilize chemically modified electrodes (CME) tailor made, for refined sensitivity and selectivity for determination of the active compounds. One of the distinctive features of CME is that it enhances the electrocatalytic activity and reduces the over potential (Zen et al. 2003).

Remarkable achievements in the field of nanotechnology and nanoscience have paved the way for improved sensitivity and selectivity of electrochemical sensors based on nanomaterials. Undoubtedly, electrode material plays a crucial role in the construction of a high-performance electrochemical sensing device. Additionally, functional nanomaterials produce synergistic effects among catalytic activity, conductivity and biocompatibility to speed up signal transduction as well as to amplify the recognition events leading to highly sensitive and selective sensing approach (Zhu et al. 2015).

Attachment of nanoparticles based materials to the electrode surface results in expansion of the true electrode surface area, proper attachment of macro, supra and biomolecules is achieved, electrochemical processes become faster, current signal is enhanced with better resolution of peaks (in case of multiple analytes). The possibility of having different kinds of shapes, of nanocrystallites, and many faces at a particular crystallite, the spatial freedom and orientation of the molecules attached to

the nanocrystals is increased. Nanomaterials with catalytic activity are required in lesser amounts thus reducing the cost of electrode. Different types of substances and materials like metals/ metal oxides and alloys, carbon nanotubes and graphene, inorganic substance polymers and nanocomposites have been employed for surface modification (Donten and Stojek, 2012).

Thus, modified electrochemical sensors have become an accepted part of analytical chemistry for they satisfy the emerging need of a simple, rapid and economic method for detection and determination of various analytes including pharmaceutical compounds (Stradiotto et al. 2003).

PRESENT STATE OF KNOWLEDGE

Role of nanomaterials in electrochemical sensors

In recent electrochemical sensing research, Nanostructured Materials (NMs) are under intense research for developing high-performance electrochemical sensors. NMs exhibit a variety of attractive physical, chemical, thermal, mechanical and electronic properties depending on their controlled size, shape and composition, which are different from their corresponding bulk states and highly desirable for EC (bio)sensor platforms (Xiao and Li, 2008). NMs integrated in EC (bio)sensor devices have played essential roles in increasing the active surface areas of electrodes, serving as multifunctional scaffolds for biomolecule immobilization, and accelerating electron transfer between electrodes and detection species, (Hayat, et al. 2014) which dramatically improve the sensing performance including the sensitivity, selectivity, and stability. Nanomaterials have been of great interest due to their electrical conductivity, unique structural and catalytic properties, high loading of biocatalysts, good stability and excellent penetrability (Wang et al. 2008). Many kinds of nanoparticles, such as metal, oxide and semiconductor nanoparticles have been used for constructing electrochemical sensors and biosensors, and these nanoparticles play different roles in different sensing systems.

Metal/Metal Oxide Nanoparticles

The most promising materials for the electrode synthesis are metal, metal oxides and their hybrid nanocomposites (Zhu et al. 2015). Gold and platinum are the most commonly employed nanoparticles for enhancing the rate of oxidation reactions. Ohsaka and coworkers (2004) developed an electrochemical sensor for selective detection of dopamine in the presence of ascorbic acid which resulted in the decrease in the oxidation over potential of ascorbic acid and effective separation of oxidation potentials of ascorbic acid and dopamine thus leading to selective detection of dopamine (Raj et al. 2003). Some non-metal nanoparticles such as oxide nanoparticles possess special catalytic properties and due to these properties they have found suitable applications in electrochemical analysis systems. Recently, various researchers have reported the use of bimetallic nanoparticles. Catalytic fine-tuning, resulting from complimentary and synergistic effects of bimetallic nanoparticles, can be achieved by the integration of a second metal nanoparticles onto a catalytic structure (Rick et al. 2016). Cao and coworkers successfully achieved high sensitivity and specificity

for glucose detection by integrating bimetallic Pt-Cu nanochains. This enhancement of sensitivity and specificity can be attributed to connectivity among dispersed crystals, porous nanostructure, clean surface and synergistic electronic effects of the constituent atoms of the bimetallic nanoparticle (Cao et al.2013).

Carbon and its Nanomaterial

Carbon based nano-structured materials like graphite, graphene etc have been employed extensively in electrochemical sensors. The carbon nanostructures alone as modifier are very active due to their developed surface and specific structure. The application of carbon nanotubes has led to better resolution of the peaks and resulted in lower detection limits in electroanalysis using voltammetry (Chen et al. 2010; Li et al. 2012; Zhou et al. 2011). Recently, graphene has become popular for surface modification of electrodes. Graphene holds properties of a promising electrode material due to its excellent electrochemical properties. Several electrochemical sensors based on graphene and its composites have been developed. In comparison with carbon nanotubes, graphene exhibits potential advantages of low cost, high surface area, ease of processing and safety (Luo et al. 2006).

Nanocomposites

It is well known that electrode material plays a crucial role in the construction of high-performance electrochemical sensing platforms for detecting target molecules by various analytical methods. Nanocomposites lead to generation of many exciting materials with new properties. If two or more different kinds of nanoparticles, having different electrochemical properties and behavior, are mixed in some specific ratio, they form new types of material known as nanocomposites. When compared, to the properties of nanocomposites divulge interactive improvements over those of the individual parent constituents. Therefore, nanocomposites have found their large applications in many fields, including development of sensors (Okpala 2014). The mixing of nanoparticles like chitosan (A. Rampino et al. 2013), zirconium oxide (Suresh S. et al. 2016), copper oxide etc and various other materials in appropriate ratio offers an improvement in the electrochemical processes. The nanocomposites have higher surface to volume ratio than the materials from which they are synthesized. The betterment of the properties of these nanocomposites is attributed to the enhanced mechanical properties, barrier properties, thermal properties and flame retardant properties (Okpala 2014). The materials resulted

from the combination of two or more different constituent materials shows entirely different properties, perhaps which could not be noticed in the parent materials. The materials composed by layering a conducting polymer over graphene (Conducting Polymer/Graphene) are reported for their excellent electrical conductivity. Gao and coworkers developed over oxidized polypyrrole/graphene deposited onto GCE for quantitative detection of adenine and guanine. The sensor showed improved sensitivity and selectivity with low background currents (Gao et al. 2014).

Conducting Polymers

Electrode modification with biomolecules, polymers or nanostructured materials has been achieved through various techniques. The most recurrent and simple one is drop casting; however, other methods, such as electro-deposition, chemically induced polymerization and self-assembling, have also been used. Nano-dimensional conducting polymers have emerged as another class of potentially beneficial material for electrochemical sensor and biosensor platforms. Metallic nanoparticles in combination with conducting polymer (CP) nanoparticles have shown greater conductivity and more rapid electrochemical switching speeds (Innice and Wallace, 2002). Recently Tawiah and his coworkers works on Polymerization-based amplification in paper immunoassay in which they use poly(ethylene glycol) diacrylate (PEGDA), triethanolamine (TEA), 1-vinyl-2-pyrrolidinone (VP) type conducting polymers (Tawiah et al, 2015).

Electrodes

GCE

GC electrodes are fabricated using glassy carbon materials which is quite reliable, high in quality and reproducibility. The low cost and broad applicability of carbon electrodes have driven years of research and electrochemical phenomenon, particularly adsorption, heterogeneous electron transfer and surface stability. Recently there is a new scenario of modification of electrode in which nanocomposite materials were used in GC electrodes to yield surfaces with low oxides contact or lack specific oxide functional group. Modified glassy carbon electrodes have much better sensitivity, selectivity, with quantitative determination of pharmaceutical drugs (Peihong Chen and Richard L. McCreery, 1996; Zhuang et al. 2016). The modification of GCE will be carried out with the different nanocomposite materials like metal/metal oxide and polymers.

CPE

CV and SWV of pharmaceutical drugs with improved sensitivity, selectivity, antifouling property and good electrocatalytic activity towards the oxidation and reduction of analyte is determined by using modified CPE. Ganesh and Kumara have reported about the comparision between mCPE and BCPE then the limit of detection of folic acid (FA) is 18.8 nm by CV technique, which is comparatively much lower than other reported methods. The modified electrode can also be used for the simultaneous determination of uric acid and folic acid in a physiological pH of 7.4. A simple modification procedure was reported for the development of electrochemical sensor or biosensor for folic acid (Ganesh and Kumara, 2016).

Electroanalytical methods

According to a hypothesis the biological reactions occurring in the body and the electrochemical reactions over the surface of electrode share similar norms. The understanding about the redox properties of drugs can give us an insight about its in vivo mechanisms. Hence, voltammetry studies can be used potentially to determine the electrochemical aspects of various pharmaceutical drugs (Gupta et al. 2011).

Among various electroanalytical techniques, Voltammetry is a method which is used to assign the current voltage measurement at a given electrode. In voltammetry, Polarography is a special case where DME is used for current-voltage measurements (Heyrovsky 1922). Another important type of voltammetry method is stripping analysis which makes it possible to determine trace concentration of the analyte up to sub-nanogram and picogram levels (Ellis and West, 1975; Nickelby and Kooke, 1957; Mars and Shain, 1957; Fargahly et al. 2014; Topal et al. 2010).

CV and SWV are perhaps the most multifaceted electroanalytical technique used for the study drugs in raw materials and pharmaceuticals (Uslu et al. 2001; Guo et al. 2004; Acuna et al. 2002) which gives us redox behavior of the analyte over a wide potential range. SWV is another achievement in the field of electroanalytical chemistry with high speed with an effective scan rate of $500mVs^{-1}$. It has been reported that square wave voltammogram can be obtained in just a few seconds as compared to the pulse techniques which takes about 3 min (Borman 1982). But it cannot be denied that pulse techniques offer low instrumentation cost with easy applicability and availability. Differential Pulse

Polarography/Differential Pulse Voltammetry is often a choice for drug analysis as it can give limit of detection as low as 10^{-8} M (Gupta et al. 2011). This technique has been used extensively for the trace determination of electroactive compound in pharmaceuticals (Kilic et al. 2006; Nigovic and Simunic, 2003; Radi et al. 2005; Shahrokhian et al. 2005; Radi and Elmogy, 2005; Jain et al. 2010; Belgaied and Trabelsi, 2002; Adhoum and Monser, 2005; Fiorucci and Cavalheiro, 2002) and biological fluids (Farhadi and Karimpour, 2007).The stripping analysis is the foremost known technique for trace analysis which includes a pre-concentration step (Wang 1988; Kissinger and Heineman, 1996; Smyth and Vas, 1992). The stripping analysis offers the following advantages of low detection limit, low determination limit, high sensitivity, wide spectrum of analytes, simplicity, low cost and least interference from the matrix (Gratteri et al.1992; Wang et al. 1999; Farghaly et al. 2000).

An accelerated growth in development of pharmaceutical compounds has rapidly started since the past decades. Medicinal chemists, pharmacologists, biochemists, analytical chemists and medical professionals have led the way with an ultimate objective to combat human diseases. In this effort, the chemical purity of the drug in all its forms is extremely crucial and vital. Thus, synthesis and characterization of such molecules and their analysis becomes important to create preliminary safety and therapeutic efficacy data which helps in further investigations.

LIST OF SOME PHARMACEUTICAL DRUGS STUDIED ELECTROCHEMICALLY WITH DIFFERENT WORKING ELECTRODE:-

A detailed literature survey about the pharmaceutical drugs being analyzed voltammetrically with different types of chemically modified electrodes along with their limit of detection has been concisely presented in the table.

PHARMACEUTICAL DRUGS (Analyte)	**Electrode**	**DETECTION METHOD**	**LOD/LOQ**	**REFERENCE**
Carbendazim	Fullerene/MWCNT/Nafion/GCE	SWV	1.7×10^{-8} mol/L	Teadoum et al, 2016
Amantadine	mGCE	DPV	15 ng/ml	Dominguez and Hernandez, 2015
Dopamine, Ascorbic Acid and Uric Acid	Lignin/GCE	CV	1.4×10^{-5} M.	Vishwanatha et al, 2015
Ondansetron	MWCNTs-Nafion/GCE	AdSV	3.1×10^{-8} M	Nigović et al. 2014
Simvastatin	p-tol/sulfonic acid/GCE	CV	$1.5 X10^{-7}$ M	Deepal et al. 2013
Methotrexate	MWCNT/GCE	DPAdSV	$3.3x10^{-8}$ mol/L	Oliviera et al. 2013
Glucose	Nafion/PtPd-MWCNTs/GCE	CV	0.031 mM	Chen et al. 2012
Tranexamic acid	GR/Bi2O3/GCE	CV & SWV	15.05 µg/ml	Shrivastava et al. 2012
Loracarbef	GCE	AdSV	$6x10^{-6}$ to $2x10^{-4}$ M	Topal et al. 2009

PHARMACEUTICAL DRUGS (Analyte)	**Electrode**	**DETECTION METHOD**	**LOD/LOQ**	**REFERENCE**
Folic Acid, Uric acid	Poly/CPE	CV	1.88×10^{-8} M	Ganesh and Kumara, 2016
Methyldopa	Fe:Co nano-alloy (Fe:Co/NL/CPE)	SWV	0.03 Mm	Gupta et al. 2015
Dopamine	AuPt/GR/CPE	DPV	0.1 μM	Zhao et al. 2015
Metformin	Pyrogallol/CPE	CV and DPV	6.63×10^{-8} mol/L	Attia et al. 2015
Dropropizine	CPE	DPAV	0.046 ug/ml	Zayed and Arida, 2015
Enalapril	MWCNT/CPE	SWV	0.81 μmol/L	Valezi et al. 2014
Sulfasalazine	MIP/CPE	DPV	4.6×10^{-9} mol/L	Sadeghi et al. 2012
Captopril	mCPE	SWV	9.1×10^{-8} M	Maleh et al. 2010
Pyridoxine HCl	mCPE	DPV	0.4l gm/L	Desai et al. 2008

OBJECTIVES

This synopsis work is proposed for the detection of pharmaceutical drugs. These drugs possess some important therapeutic properties. The aim of the research work comprises of the following objectives:

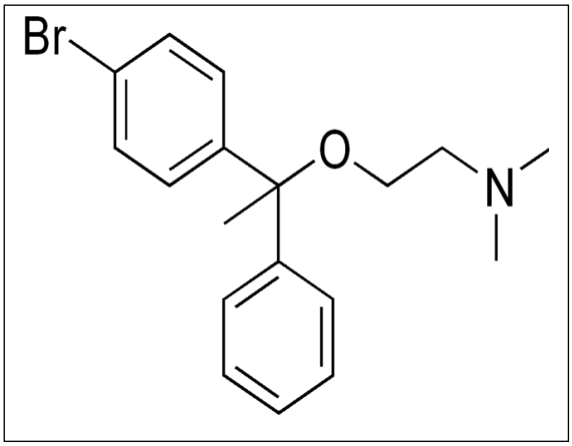
- Synthesis of the nanocomposites based on metal/metal oxide and polymers. (Chitosan, dextrin, CNTs, Graphene, Graphene Oxide, ZrO, CuO, TiO_2 etc.)
- Characterization of the prepared nanocomposites using techniques such as XRD, FTIR, SEM, and UV-VIS spectrophotometry.
- Fabrication of electrodes (GCE, CPE, etc) with the synthesized nanocomposites.
- Electrochemical characterization of the modified electrode using cyclic voltammetry and electrochemical impedance spectroscopy (EIS).
- Study of voltammetric behavior and mechanistic aspects of pharmaceutical drugs: **Embramine, Metadoxime, Cyclobenzaprine, Butorphanol.**
- Standardization of the optimum conditions with special reference to effect of pH, Potential and scan rate, nature of surfactants and drug stability using Cyclic and square-wave voltammetric techniques.
- Validation of the methods in terms of sensitivity, limit of detection, limit of quantification, accuracy, precision and specificity.

PHARMACEUTICAL DRUGS UNDER STUDY

1- EMBRAMINE:-

IUPAC –

- 2-[1-(4-bromophenyl)-1-phenylethoxy]-*N, N*-dimethylethanamine



THERAPEUTIC PROPERTY –

- Antihistamine and anticholinergic

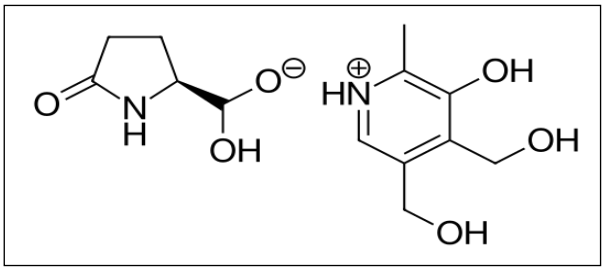
TRADE NAME -

- Embramine (OS: BAN)
- Mebrophenhydramine (IS)

2- METADOXIME:-

IUPAC –

- L-Proline, 5-oxo- compd. with 5-hydroxy-6-methylpyridine-3,4-dimethanol



THERAPEUTIC PROPERTY –

- Anti-alcohol or antabuse

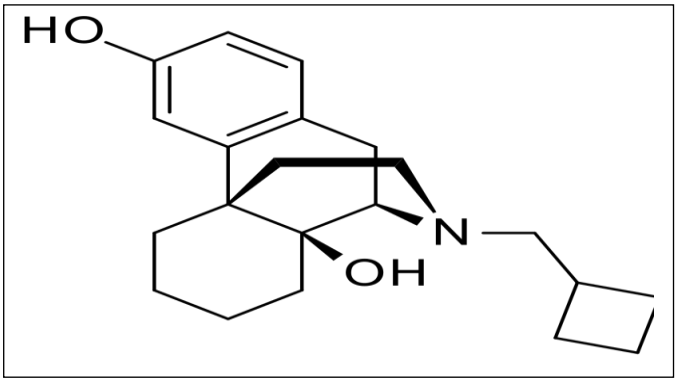
TRADE NAME –

- Alcohep, Viboliv, Extol, Alcoliv, Livopill, Somaliv, Metadoxil.etc.

3- BUTORPHANOL:-

IUPAC –

- 17-(cyclobutylmethyl) morphinan-3, 14 - diol 2,3 -dihydroxybutanedioate



THERAPEUTIC PROPERTY –

- Analgesic

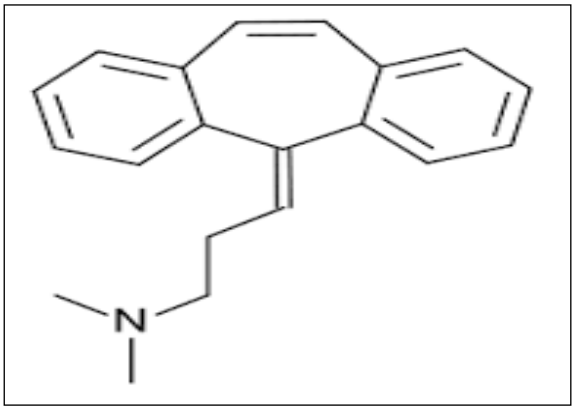
TRADE NAME –

- Stadol

4- CYCLOBENZAPRINE:-

IUPAC –

- N-dimethyl-3-(dibenzo-cyclohepten-5-ylidene) propylamine



THERAPEUTIC PROPERTY -

- Muscle relaxants

TRADE NAME –

- Amrix, Fexmid, Flexeril etc.

SELECTION CRITERIA OF PHARMACEUTICAL DRUGS

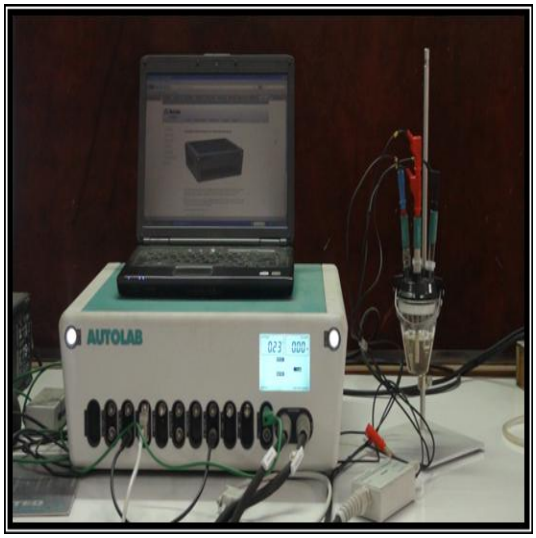
- A detailed survey of literature revealed that the chosen drugs have not been explored voltammetrically yet.

- The pharmaceutical drugs selected offer important therapeutic properties.

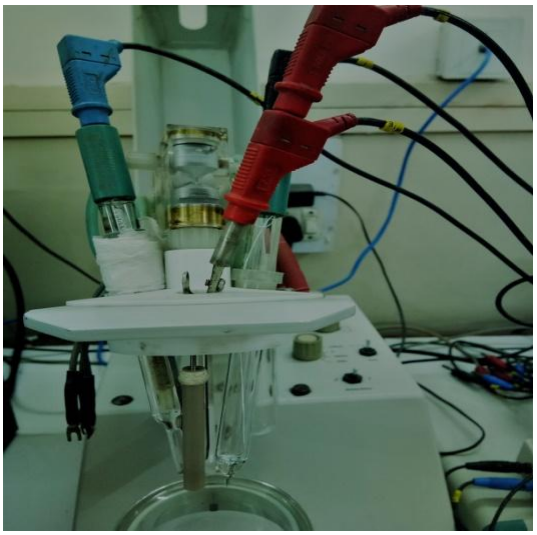
- The drugs were found to be electro active in nature which is an important criterion for electrochemical analysis.

INSTRUMENTATION:-

A potentiostat (Autolab PGSTAT 302N, Metrohm, Netherlands) will be used to carry out electrochemical voltammetric studies. NOVA (version 1.11) will be used as interface for the system:-



AUTOLAB PGSTAT 302N



Three Electrode system

Ag/AgCl ELECTRODE (REFERENCE ELECTRODE)

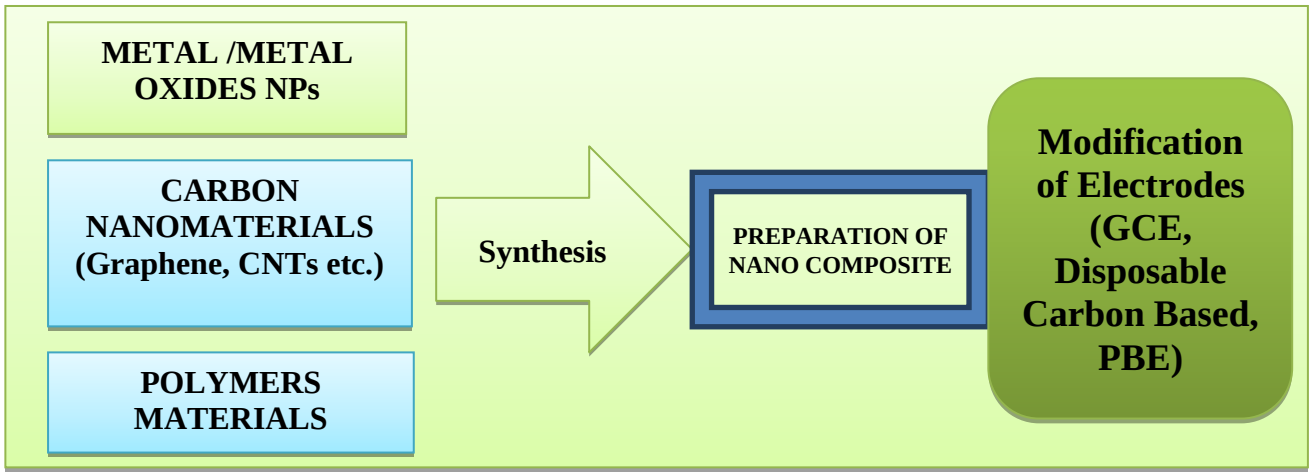
Pt ELECTRODE (COUNTER ELECTRODE)

METHODOLOGY:-

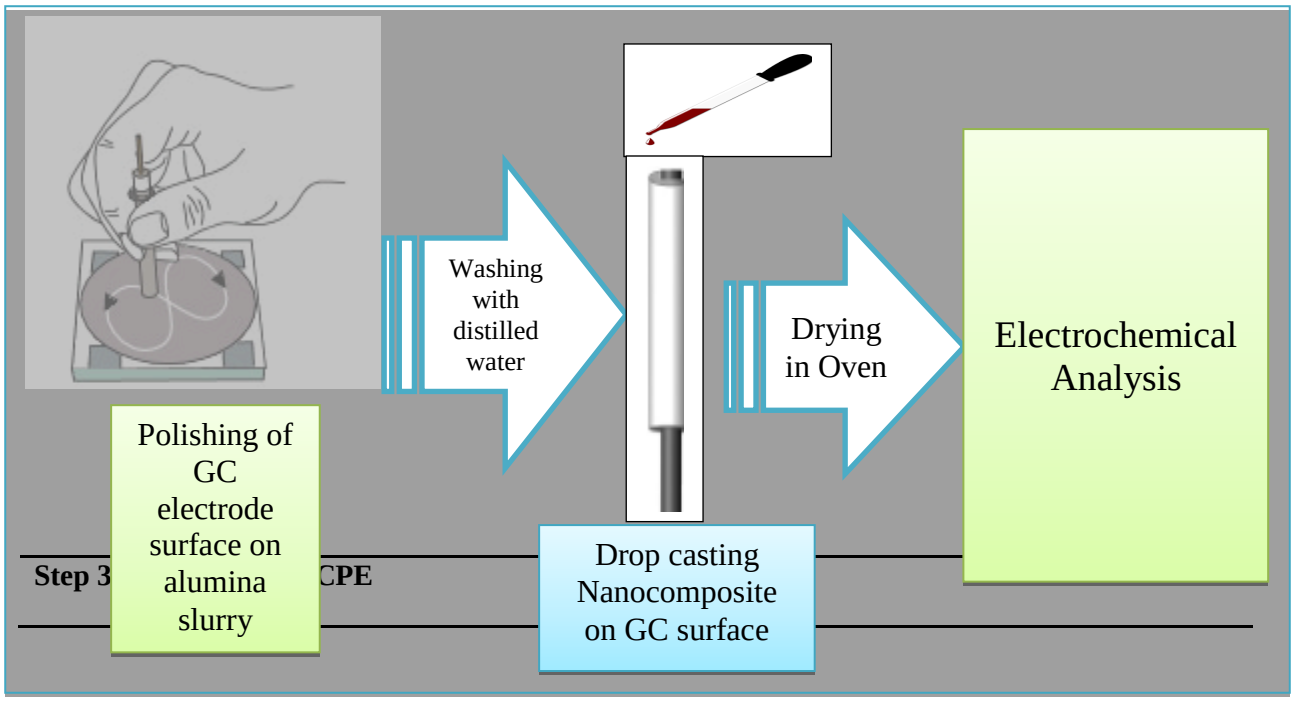
The work will be carried out using standard protocol and procedures reported in literature for the voltammetric analysis of drugs at nanocomposites modified electrodes.

Proposed plan of work is depicted schematically as follows -

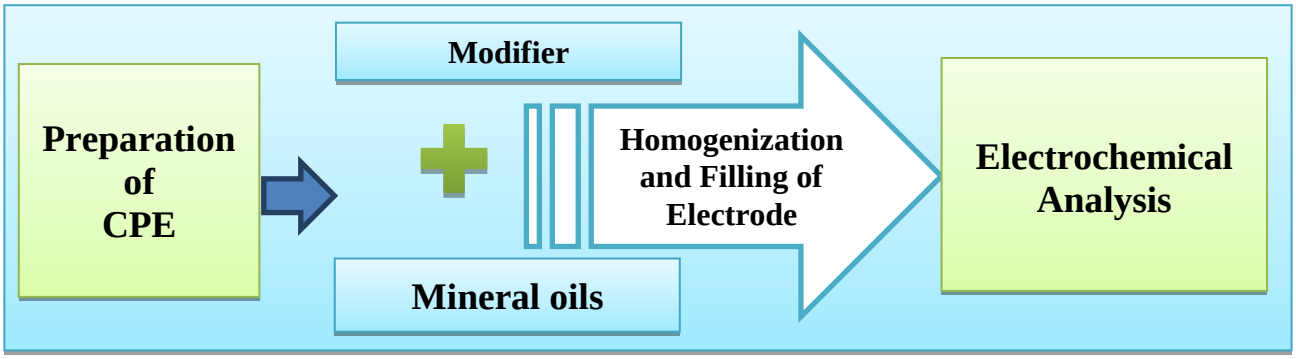
Step 1- Preparation of Nanocomposites for Chemical modifications of the electrode


METAL /METAL OXIDES NPs
CARBON NANOMATERIALS (Graphene, CNTs etc.)
POLYMERS MATERIALS
Synthesis
PREPARATION OF NANO COMPOSITE
Modification of Electrodes (GCE, Disposable Carbon Based, PBE)

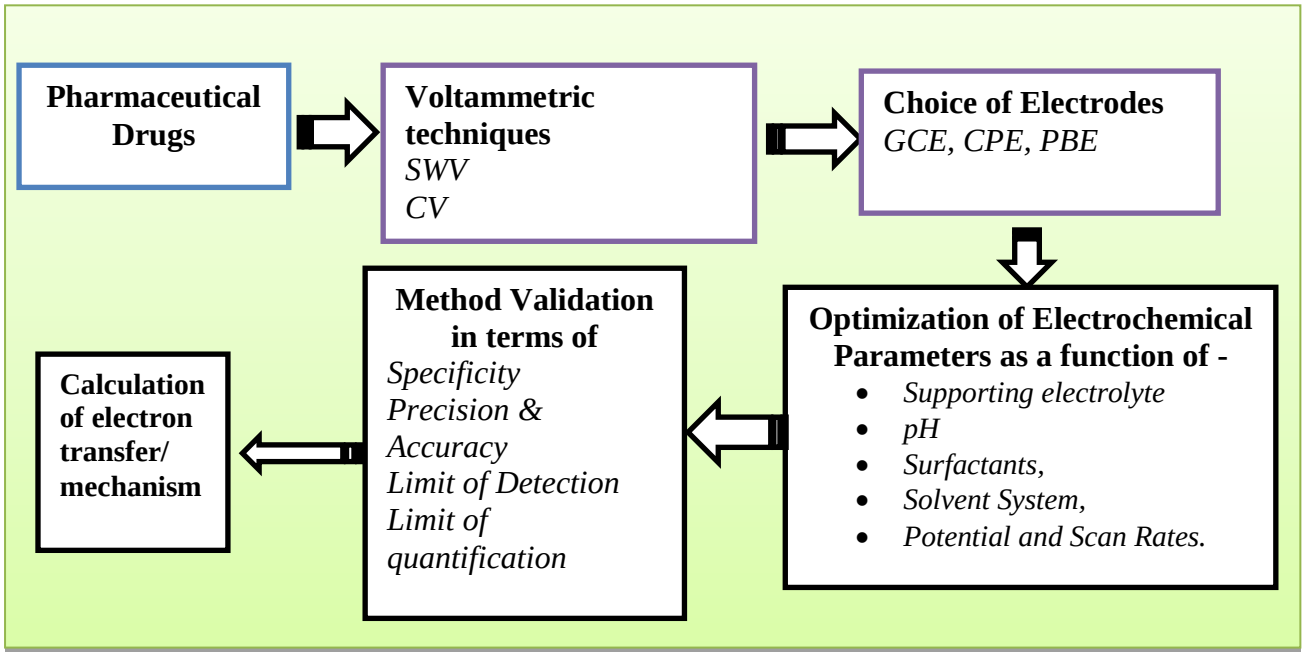
Step 2- Fabrication of GCE


Polishing of GC electrode surface on alumina slurry
Washing with distilled water
Drop casting Nanocomposite on GC surface
Drying in Oven
Electrochemical Analysis

Step 3 **CPE**



Step 4- Standardization and optimization of electrochemical parameters for the evaluation of electrocatalytic response of pharmaceutical drugs under study.



SIGNIFICANCE OF THE PROPOSED WORK

The understandings of pharmaceutically active compounds' redox properties are evaluated by electroanalytical technique which can lead to development and growth in the field of pharmacology.

- **Alternative Analytical Approach:-** New analytical method developed for the elucidation of mechanistic aspects of the chosen pharmaceutical drugs.

- **High Sensitivity And Specificity:-** Voltammetric study of the pharmaceutical drugs provide an edge over the existing analytical methods on the basis of high sensitivity, specificity and lower limit of detection of the fabricated sensors towards the analyte system. Further it also provides the advantage of low solvent complexity, cheaper instrumentation and ease of handling.

- **Drug Control:-** Fabrication of Nanocomposite based sensors for the electrochemical study of the analyte system, thereby delivering, an effective alternative approach in the drug control.

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